Review Article

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A Review on Monkey Pox: From Pandemic to Endemic

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Abstract

Monkeypox is a rare viral disease that has been identified as a potentially emerging infectious disease with the potential to cause outbreaks and epidemics. The virus is closely related to the small pox virus and belongs to the family Poxviridae. Monkey pox is primarily found in Central and West Africa, where it is transmitted to humans through contact with infected animals or humans. The virus can cause a range of clinical manifestations, from mild flu-like symptoms to severe illness with high mortality rates. The clinical presentation of monkey pox typically starts with fever, headache, muscle aches, and fatigue, followed by the development of a rash that spreads across the body. The rash progresses from macules to papules, vesicles, pustules, and scabs over several weeks. In severe cases, complications such as pneumonia, sepsis, and encephalitis can occur. There is currently no specific treatment for monkeypox. Supportive care measures such as hydration and pain management are used to manage symptoms and prevent complications. Vaccination against smallpox has been shown to provide some protection against monkeypox; however, it's effectiveness against the virus remains unclear. The prevention of monkeypox relies on measures such as avoiding contact with infected animals or humans and practicing good hygiene practices such as hand washing. Early detection of cases through surveillance systems is also crucial for preventing outbreaks. In conclusion, monkeypox is an emerging infectious disease that poses a significant public health threat in endemic regions. Continued research efforts are needed to better understand the epidemiology and pathogenesis of the virus and develop effective prevention strategies such as vaccines or antiviral therapies.

Keywords: Monkeypox; Virus; Zoonotic disease; Emerging infectious disease; Clinical manifestations; Treatment; Prevention; Vaccination.

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INTRODUCTION

As the world is overcoming with the Covid-19 pandemic, monkeypox poses a risk for yet another pandemic. Monkeypox, caused by the monkeypox virus belonging to the Orthopoxvirus genus of the Poxviridae family, was first observed in a human in 1970. Since then, it has been endemic in various regions of Africa. However, the monkeypox cases have been rising all around the world now,

imported humans and potential monkeypox host animals being the major cause of the same. This brick shaped or oval shaped virus with a double stranded DNA genome enveloped with a lipoprotein envelope shows clinical manifestations similar to that of a smallpox infection. The size of the monkeypox virus ranges between 200 and 250 nm consisting of 196,858 base pairs. Since the majority of the cases of monkeypox reside in Africa, the virus has been differentiated into two different clades depending on their geography, epidemiology and clinical features, namely Congo Basin clade and West African clade. The virus can infect an individual, either by animal-to-human transmission or human-to-human transmission. Living near the woods, sleeping on the floor etc. can be some of the causes of animal-to-human transmission, while human-to-human transmission mainly is caused by respiratory droplets or contact with the fluids of lesions. The monkeypox infection shows as a flu-like illness with swollen lymph nodes but progresses to a rash that develops all over the body. Avoiding transmission tracts and getting the licensed smallpox vaccines have been thought to prevent monkeypox. No specific treatment exists for monkeypox, however, side treatments to treat the symptoms are usually used to control the infection. With the rapid increase in the number of monkeypox cases, it poses a risk of turning from an endemic to a pandemic.

NATURE

Taxonomy

Monkeypox virus, causative of monkeypox, belongs to the *Orthopoxvirus* genus of the *Poxviridae* family.[1] The Poxviruses are also known as ancient viruses since they have been believed to form visible "pox" in insects, mammals, reptiles and birds, before the division of vertebrates and invertebrates. The *Poxviridae* family is subdivided into two subfamilies on the basis of the host they infect. The *Chordopoxvirinae* subfamily infects vertebrates and consists of 18 genera, namely Avipoxvirus, Capripoxvirus, Cervidpoxvirus, Leporipoxvirus, Molluscipoxvirus, Orthopoxvirus, Parapoxvirus, Suipoxvirus, and Yatapoxvirus while the *Entomopoxvirinae* subfamily infects non-vertebrates and consists of 4 genera, namely Alphaentomopoxvirus, Betaentomopoxvirus, Deltaentomopoxvirus, and Gammaentomopoxvirus. The classification of these subfamilies of *Poxviridae* family into their genera is done on the basis of phylogenetic grouping, induction of their immunological cross protection as well as their shared antigenic resemblance.[2]

Structure

Poxviruses are either brick shaped or oval shaped and are enveloped by a lipoprotein consisting of a double stranded DNA genome. They measure between 200-400nm when observed under the electron microscope. Having structure similar to that of other Orthopoxviruses, monkeypox virus is seen to be ranging between 200 and 250 nm in size. The outer membrane shelters the double stranded DNA genome, the enzymes present in a densely packed core as well as the transcription factors. The core containing the enzymes is biconcave in shape and consists of lateral bodies on both sides.[1,2] It has a dumbbell shaped core along with lateral bodies which is slightly pleomorphic and is enveloped.[3]

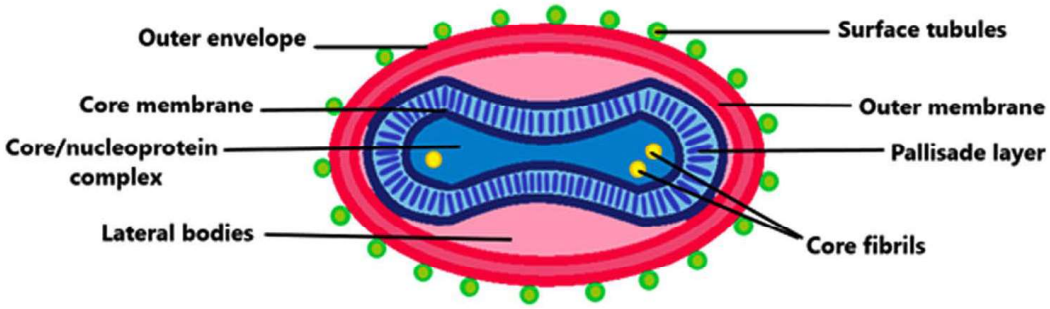

Fig. 1: Sturcture of Monkeypox virus

Genome

The genome of monkeypox virus consists of 196,858 base pairs (bp) with 190 open reading frames (ORF) that includes 60 amino acid residues or more. Like other orthopoxviruses, the monkeypox virus consists of a number of factors and enzymes necessary for viral entry, replication as well as maturation. Viral replication is governed by highly conserved genes present in the central region of the

genome while the virus-host interaction is carried out by the terminal less conserved genes.[4] The genome of Orthopoxviruses consist of a terminal inverted repetition [ITR] which is a similar but inversely oriented sequence. It is a 6379-bp ITR.[5] The ITR includes terminal hairpins and a set of short tandem repeats. The sequencing of a recent MPV isolate's DNA (MPV-ZAI) (strain: ZAI-96-I-96) portrays that it consists of a 7379-bp ITR. All the essential genes present in all other Orthopoxviruses are present in MPV and are located in the central region of the genome (ORFs C10L to A25R) having more than 90% sequence identity with the genomes of other Orthopoxviruses. Four ORFs present on the left side of the MPV-ZAI genome are situated within the ITR. It's counterparts are present on the right side of the genome.[5] Different strains of monkeypox differ from each other on the basis certain number of single-nucleotide polymorphisms.[6]

TWO CLADES OF MONKEYPOX

There are two distinct clades of monkeypox that exist: The Congo Basin Clade viruses and West African clade viruses. Both the clades have geographical, clinical and epidemiological differences.[7] Human monkeypox caused by the Congo Basin clade shows initial symtoms similar to that of smallpox followed by an asymptomatic incubation period of two weeks and thereafter development of fever along with rash spread across the entire body. The Congo Basin monkeypox is easily transmissible across humans and can prove to be fatal with a fatality rate of around ~10% in non-vaccinated population. It is more morbid as compared to the west African clade.[8] The west African clade is less severe and shows less human to human transmission in comparision to the Congo Basin clade. However, the strains of both the clades show 99% sequence similarity.[9] The reason behind the reduced virulence of the West African clade is the presence of deletions and fragmentations in its open reading frames. It is also due to the fact that the gene responsible for inhibiting the complement enzymes which is an important immune-modulating factor is absent in West African clade viruses. Furthermore, the Congo Basin clade viruses prohibit the production of cytokine in human cells by preventing the activation of receptor-mediated T-cells. It was also observed in certain transcriptional studies that there was silencing of the transcription of specific genes that were involved in host immunity in the Congo Basin clade viruses.[10]

EPIDEMIOLOGY

Transmission

Reproductive ratio (R0) is a term that refers to the degree of transmissibility of a disease. The R0 value of monkeypox is reported to be between 1.10 and 2.40. This means that every infected individual has the ability to infect one or two other individuals. Furthermore, it also suggests that an epidemic of monkeypox can be expected in imported animal or human cases.[11] Monkeypox has been suspected to be transmitted in humans via two routes: human-to-human and animal-to-human. Close contact with infected humans such as sharing the same food/drink, living in the same household etc. lead to human-to-human transmission of the disease. This is due to the fact that the disease transmits through the aerosols or through direct contact with the fluids exudated through the lesions of infected individuals.[12] A significant number of cases have also been observed in gays and bisexual individuals.[13] The main risk factor for animal-to-human transmission includes living near woods, visiting the forest, sleeping on the ground, being touched or scratched by an infected animal etc.[14] The most common hosts for this disease includes rodents such as mice, hamsters, squirrels and porcupines.[15] Initially, prairie dogs which were housed with rodents were thought to be the main cause of monkeypox.[16]

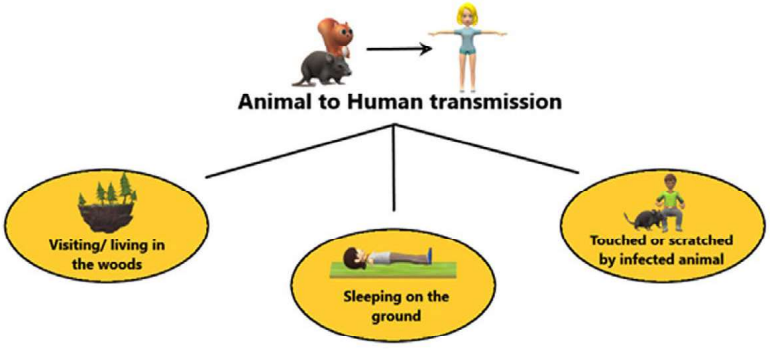

Fig. 2: Animal to human transmission of monkeypox virus

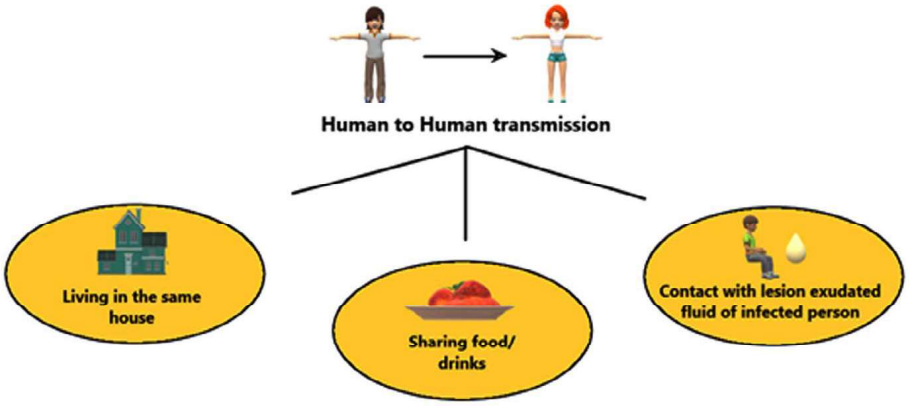

Fig. 3: Human to human transmission of monkeypox virus

Geographical Distribution and Prevalence

The first ever case of monkeypox was observed as a pustular rash illness in cynomolgus macaques (Macaca fascicularis) being transported from Singapore to Copenhagen in 1958. Monkeypox, hence was named after its first described host.[15] The first human monkeypox virus case was observed in 1970 in Democratic Republic of Congo when a 9 month old child showed skin lesions similar to that of smallpox. In the years between 1970 and 2000, approx. 404 confirmed and 500 suspected cases of monkeypox in humans were observed in different countries of Africa. Thereafter, cases of monkeypox were being observed all over the world, although the highest number still existed in Africa.[17,18] Isolates tested from outbreaks in different countries such as Cameroon, Gabon, DRC and Republic of Congo comprised of the Congo Basin clade whereas isolated imported to United States of America from Ghana comprised of the West African clade.[19] Monkeypox seems to be rising in the current years following 2022 in countries such as Spain, UK, India, Portugal and USA.[13] As of July 1, 2022, 5783 cases of monkeypox were distributed among 52 different countries worldwide, as confirmed by the Centre of Disease Control and Prevention (CDC). The majority of the confirmed cases were seen to be prevalent in humans below the age of 40. It has also been observed that more number of cases exist in males, however, the reason behind the same is unknown. This surge in the number of monkeypox cases has been observed after the discontinuation of the small pox vaccine which helped provide cross-protective immunity.[20,21]

PATHOGENICITY

Monkeypox usually shows as a flu-like illness followed by swollen lymph nodes which progress to rash all over the body and face. The incubation period of the virus usually lasts from 6 to 21 days followed by a febrile stage of 1 to 4 days and a rash stage of 2-4 weeks. The rash being similar to chickenpox or syphilis leads to misdiagnosis of the disease. The disease usually shows symptoms such as fever with a temperature of more than 38 degrees Celsius, a sore throat, mouth sores, pain in the muscles and back, fatigue, chills and lymphadenopathy-axillary, inguinal, cervical and preauricular. There can be severe complications such as pneumonitis, encephalitis, keratitis, conjunctivitis, dermatitis etc.[22] The rate of host cell protein inhibition of Monkeypox virus is more rapid as observed in other Orthopoxviruses.[23] A set of molecules enveloped with virulence genes are present in Orthopoxviruses in order to elude the immune system of the host. These proteins can be characterised into categories based on their location of function, i.e. intracellularly or extracellularly. The intracellular proteins can be further subdivided into virostealth and virotransducer proteins whereas the extracellular proteins consists of one type of protein, namely viromimic protein. The virotransducer proteins help in preventing the cell from responding to the infection by interfering with the apoptotic pathways and oxidative burst. The virostealth proteins, Furth more, help in preventing the detection of the virus by downregulating the major histocompatibility complex class 1 (MHC 1) and CD+4, which are important molecules needed for immune recognition. The viromimic protein, that is present extracellularly can be classified into two categories, namelyviroreceptors and virokines. The viroreceptors are involved in the competitive binding of the cytokines and chemokines of the host and present on the surface of the cell as glycoproteins. The virokines on the other hand, fabricates viral mimics of cytokines, chemokines and growth factors present in the host which help in overthrowing the host immune response which

is malignant to the survival of the virus as well as helps promote suitable responses for the replication and spread of the virus. The simultaneous working of these modulatory proteins helps the virus evade the immune response and replicate in the host.[24,25,20,21]

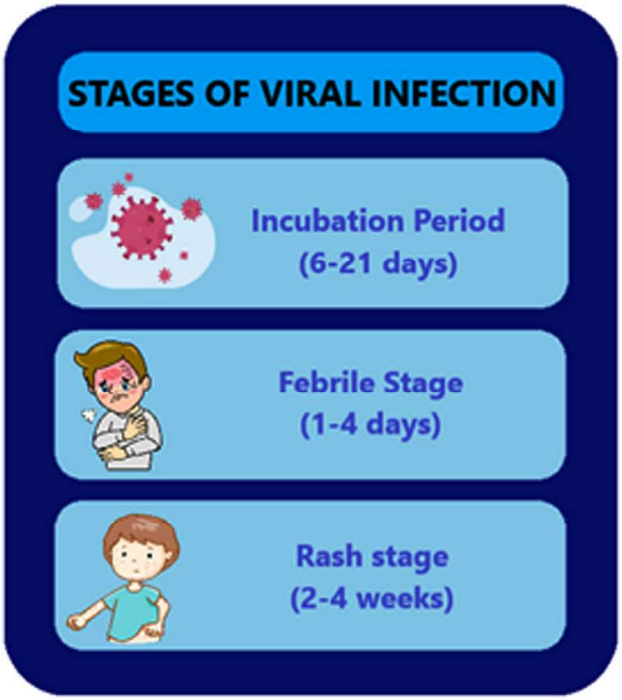

Fig. 4: Pathogenesis of monkeypox virus

Virion Polypeptides

Orthopoxviruses have their polypeptide profile in molecular weight region around 30,000 to 40,000.[26] One of the main characteristics of the monkeypox virus is the presence of p22 and p24 polypeptides absent in all other poxviruses and the absence of p23 polypeptide found in other poxviruses. Although the monkeypox strains of human and monkeys are believed to be homogenous, minor differences in both structural polypeptides and DNA endonuclease fragments are observed. One of the major difference found in the monkeypox strains of humans and monkeys is that the former strain consists of P54 whereas the latter contains P53. This difference holds importance since P53, being a surface component is removed by NP40 (mild non-ionising detergent which releases loosely bound polypeptides) but no change is there in the human monkeypox strain.[27]

Replication

DNA viruses are usually known for replicating in the nucleus of the host cell, using the cellular proteins, However, the genome of poxviruses replicates in the cytoplasm of the host cells (vertebrate or invertebrates) as they use virus-encoded proteins for their replication process. The important functions of transcription and virus assembly are carried out by the central part of the genome. The replication process of poxviruses is not rapid due to it's large size. In addition, it's large size makes the immune system of the host cautious and hence it's survival within the host becomes difficult.[28] The replication cycle of poxviruses does not differ greatly from that of other viruses. They too, consist of proteins that help regulate the processes of cell binding, membrane fusion and entry. In the case of poxviruses, there exist two types of virions, mature virion (MV) and Extracellular enveloped virion (EV). MV consists of a single membrane while EV consists of an additional outer membrane. Both the membranes are disrupted before the fusion. MV consists of four viral proteins associated with it, which help in the binding of laminin or glycosaminoglycans on the cell surface, thus facilitating the attachment of MV onto the host cell. Irrespective of the infection being MV or EV mediated, 11 to 12 non-glycosylated, transmembrane proteins, ranging between the size 4 to 43 kDa are responsible for the fusion of the virus to the host cell. MVs and EVs differ in their stability and hence their transmissibility. MVs are more stable as compared to EVs and hence are easily transmitted between host animals, whereas the presence of a fragile outer membrane in EVs, they are specialised to exist the intact cells and spread within the host body.[29–31] The cytoplasmic structures within which the entire process of the DNA replication of poxviruses is carried out were initially known as Guarnieri bodies and are now referred to as factories, each of which derives from a single infecting particle. During the initial stages of an infection, a factory exists as a compact structure surrounded by membrane within which the DNA is present. These structures drive through the rough endoplasmic reticulum (RER) of the host cell. As the synthesis of the DNA progress, the factories become larger in size and acquire a more irregular shapedue to the formation of viral mRNA and host translational factors containing cavities. On reaching the later stages of the replication cycle, a complex of late gene products and a group of viral membrane assembly proteins proceed to disrupt the neighbouring endoplasmic reticulum membranes and fabricate crescent shaped structures which act as substrates for the immature virions (IV) assembly. IVs are then processed into MVs, which are the most plenteous infectious species. These MVs finally, exit the cell by fusing

with the cytoplasmic membrane.[32,33]

PREVENTION

Previous research suggests that prior immunization using smallpox vaccines may provide protection against the monkeypox virus and help improve the clinical manifestations of the disease. It has also been observed that in addition to the decreased severity of the disease, the vaccinia vaccine may provide around 85% protection from the virus. This is due to the fact that both Monkeypox virus and smallpox virus share the same genus.[20,34]

Currently, there exists two licensed smallpox vaccines, namely JYNNEOS and ACAM2000, which can be potentially used for monkeypox as well.

JYNNEOS is a live viral vaccine and an attenuated, non-replicating orthopoxvirus obtained from modified vaccinia Ankara-Bavarian Nordic (MVA-BN strain). This vaccine is used for prevention of monkeypox in individuals above the age of 18 as they are at a higher risk of acquiring the viral disease. This vaccine is approved in different countries under different name.[35,36]

ACAM2000 too, is a live viral vaccine consisting of the vaccinia virus. It is a replication competent vaccinia virus and causes a cutaneous reaction at the site of inoculation. Hence, there lies a risk of inadvertent inoculation or autoinoculation with its usage. It is generally used to provide active immunisation in individuals that show a higher risk of contracting the virus. The Centre for Disease Control and Prevention (CDC) allows the use of ACAM2000 for non-variola orthopoxvirus infections, including monkeypox, during an outbreak, under the IND protocol. However, it is advised not to use ACAM2000 in HIV prone population.[36,37]

In addition to vaccination, CDC lists certain ways by which one can prevent monkeypox. This includes avoiding contact with certain animals that may be a potential host or any kind of material that has come in contact with an infected animal. It is also advised to avoid sick or dead animals in endemic regions. Isolation of the infected individuals, washing hands with soap or using alcohol based sanitizers and wearing of mask and gloves while dealing with an infected individual are some of the ways one can prevent human-to-human transmission.[20,38]

DIAGNOSIS

Different kinds of assays are used in order to identify the Orthopoxviruses. Swabs with lesion exudate or crust specimens are considered as the best specimens for the diagnosis. Several conventional tests are done for the diagnosis, including viral isolation, immunohistochemistry and electron microscopy. Specimens can also be analysed using polymerase chain reaction (PCR) as well as real time PCR. These assays show high sensitivity and are quite efficient in detecting the presence of viral DNA.

Viral Isolation/Culture: In this method of diagnosis, a live virus is cultured and grown from the specimen received from the patient which helps provide the definitive classification of the species. Specimen from the lesions is considered as the best specimen for this diagnosis. This diagnosis must be followed by characterisation for the identification of the virus.

Electron Microscopy: This method works on the principle of negative staining in terms of poxviruses. A brick shaped particle is observed under the microscope which aids in the visual classification of the poxviruses. However, the Orthopoxviruses share identical morphology and hence are indistinguishable. The best specimens for this diagnosis include swab material, biopsy specimen, viral culture or vesicular fluid.

Immunohistochemistry: This method of diagnosis detects the presence of antigens belonging to Orthopoxviruses species. It is useful to eliminate other suspect species, however, it is not specific for monkey poxvirus. A biopsy sample is considered the best specimen for this method of diagnosis.

PCR/ Real-time PCR: This method of diagnosis is used to detect the presence of DNA signatures that are specific to the monkeypox species. PCR uses stable viral DNA which is usually stored in a cool, dark place. Since it is highly sensitive assay, contamination should be taken care of. Lesion material from the patient is considered as the best specimen for this diagnosis.

Anti-orthopoxvirus IgG: It is a diagnosis used to detect the presence of antibodies obtained due to previous exposure to orthopoxvirus, which includes both pathogen as well as a smallpox vaccine. This assay is however not specific for monkeypox virus. Blood serum and cold chain are required for this method of diagnosis.

Anti-orthopoxvirus IgM: It is a diagnosis used to

detect the presence of antibodies obtained due to recent exposure to orthopoxvirus, which includes both pathogen as well as a smallpox vaccine. It is used for suspected patients and required blood serum and cold chain for diagnosis.

Tetracore Orthopox Biothreat Alert: It is used for the detection of Orthopoxvirus antigens and can be used to detect an active case. It is less sensitive than PCR and is not monkeypox specific. Lesion material is considered the best specimen for this diagnosis.[9, 39–42]

CLINICAL MANIFESTATIONS

Monkeypox shows a similar infectious pathway to that of smallpox that typically begins with the exposure of respiratory mucosa of the host. Once the virus enters the host cell, replication of the virus occurs at the site of inoculation. In the case of primary viremia, post viral replication, the viral load is spread to the local lymph nodes whereas, in secondary viremia, the viral load is spread to distant lymph nodes and organs. This entire process is known as the incubation period which typically lasts from 14 to 21 days.[1] The incubation period is non-contagious since no clinical manifestations are observed during this stage. The clinical manifestations and symptoms are first observed during the prodromal stage. During this stage, the individual is most infectious as the secondary viremia sets in and roots from lymphoid organ proceeding to skin and the tertiary organs including eyes, lungs, gastrointestinal tract etc. Furthermore, during this stage, symptoms such as lymphadenopathy and mucocutaneous lesions begin to appear along with other non-specific symptoms such as fever, headache, myalgia, backache, chills, exhaustion, mouth and throat ulcers and rashes. These commonly occurring non-specific symptoms are seen usually after one or two weeks of the person contracting the infection. The prodromal stage observes the triggering of the immune system due to the onset of these non-specific symptoms. This initial activation of the immune system leads to the enlargement of the lymph nodes including cervical, maxillary and inguinal simultaneously to the onset of fever. Post 3 to 4 days from the onset of fever, rashes begin to appear.[28,43] The rash usually shows itself first on the face and is then centrifugally distributed all over the body, which means the extremities and the face observe more number of lesions than the abdomen and the trunk. The oral lesions provide difficulty in eating and drinking leading to a disrupted nutrient uptake. The skin lesions, on the other hand, lead to extensive perturbation of the skin which raises concern for secondary bacterial infections.[20,44,45]

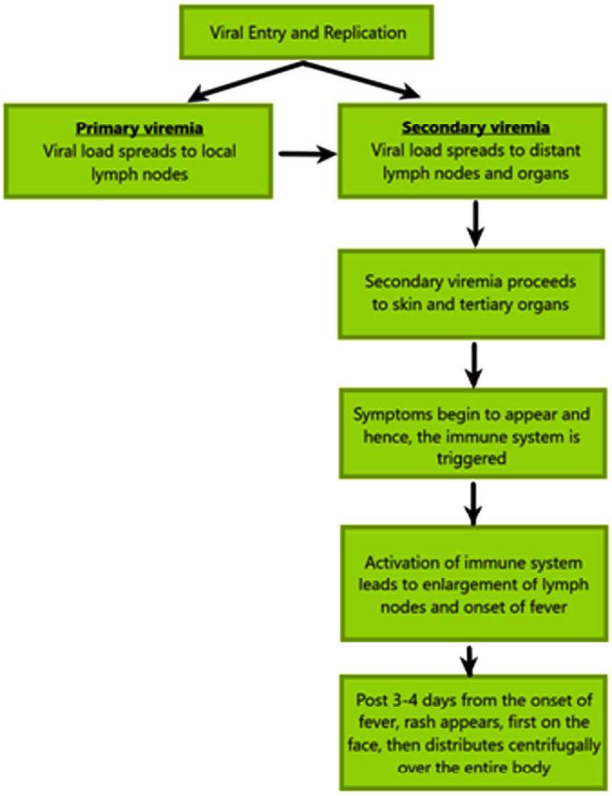

Fig. 5: Clinical manifestation of monkeypox virus

Disseminated vesiculopustular rash is the main indicator of monkeypox.[46] Before the scabs starts peeling off the rash i.e. the desquamation phase, there are several stages through which a rash goes through. It has been observed that these definite lesions are first presented as enanthem, macular and popular and then it further progresses as vesicular and pustular. It usually takes two to three weeks for these lesions to become crusted. The tongue and mouth of an infected individual will experience the first lesions and this is known as enanthem. Then, comes the macules which are flat lesions that first show appearance on the face and then spread centrifugally to arms, legs and hands and usually last from around 1 to 2 days. Papules are when these flat lesions become raised. This stage lasts for 1 or 2 days. Papules progress to become vesicles when they become filled with clear fluid. They also last for around 1 to 2 days. Pustules are when instead of clear fluid, the lesions get filled with opaque fluid. In this stage, the lesions are round, raised and firm to touch. This stage lasts around 5 to 7 days. Once the lesions have gone through all these changes, they reach the desquamation stage

when crusting takes place and the lesions peel off. Scars, hyperpigmentation and hypopigmentation are some of the abnormalities that might be observed once the scabs are peeled off. In certain cases, these lesions can progress to form 'partial-thickness wounds'. Occlusive therapies can be used to promote re-epithelialisation.[28,46,47]

TREATMENT

No specific treatment exists yet for monkeypox, however, treatments such as vaccinia vaccine, vaccinia immune globulin (IVG), cidofovir and tecovirimat, which have been useful for smallpox treatment may be used. Tecovirimat is used as an oral intracellular viral release inhibitor which has specific efficacy for certain orthopoxviruses, monkeypox being one of them. Cidofovir, on the other hand, shows antiviral effect by inhibiting the viral DNA polymerase. Except these specific treatments, supportive treatment is given in accordance to the symptoms the patient is facing. In the case of gastrointestinal problems or mouth and throat ulcers. Antidiarrheal and antiemetic medications are used alongside providing rehydration to the patient, either orally or intravenously. Bronchopneumonia or respiratory distress is relieved by the oral or intravenous injection of antibiotics, non-invasive ventilation or using nebulizers. Sepsis is treated using corticosteroids, antibiotics, supplemental oxygen and insulin. Antipyretic medications and external cooling help cut the fever. Skin lesions and scarrings are usually treated using moist occlusive dressings while superinfection skin is cured advanced wound management such as negative pressure wound therapy or incision and drainage. Inflammation leading to lymphadenopathy is controlled using anti-inflammatory medicines. Lastly, corticosteroids and antivirals/antibiotics are used to treat corneal infection. These are the ways we can manage the symptoms of a patient, however no clear treatment exists for monkeypox.[14,21,28, 36]

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